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(71) Applicant: STERWIN AG.
Zeughausgasse 9
CH-6300 Zug(CH)

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(72) Inventor: Margetts, George
44 Broomfield Drive
Billingshurst Sussex(GB)

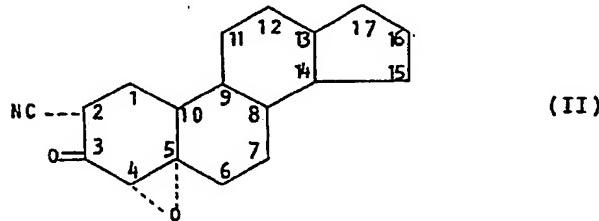
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(74) Representative: Green, Alan James et al,
Sanderson & Co. 97 High Street
Colchester Essex CO1 1TH(GB)

(54) Steroid compounds.

(57) The present invention relates to certain steroid compounds in which the particle size of the active compound is controlled in order to obtain a higher and more acceptable level of *in vivo* activity.

The steroid compounds are those having a basic ring structure of the general formula:



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In particular that known as "trilostane", the compounds being in particulate form and consisting of particles having a mean equivalent sphere volume diameter of less than about 20 µm, at least 95% of the particles having a particle size of less than about 50 µm.

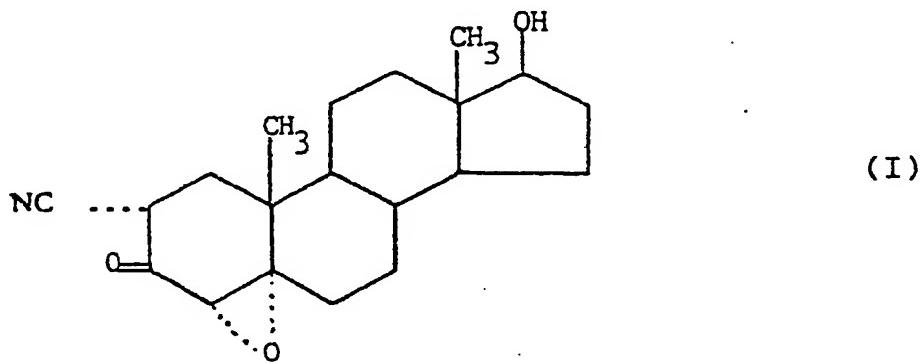
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- 1 -

STEROID COMPOUNDS

The present invention relates to certain steroid compounds, and in particular to pharmaceutical compositions comprising an active ingredient selected from those steroid compounds, in which the particle size 5 of the active compound is controlled in order to obtain a higher and more acceptable level of in vivo activity.

The present invention is concerned specifically with 2α -cyano- 4α , 5α -epoxyandrostan-17 β -ol-3-one having the formula:



10 The above compound of formula (I) has the common name "trilostane" and is described, for example, in British Patent Specification No. 1,123,770 and in U.S. Patent Specification No. 3,296,295. These earlier Specifications describe the adrenocortical inhibiting 15 properties of trilostane and related compounds, as does the article by Neumann et al in Journal of Medicinal Chemistry, 13, 948 (1970).

It is currently proposed to use trilostane as an abortifacient, and also, more importantly, in the 20 treatment of Cushing's Syndrome and Conn's Syndrome. Cushing's Syndrome is due to an increased secretion of hydrocortisone-type steroids, and Conn's Syndrome is due to an adenoma of the glomerulosa cells of the adrenal cortex, with which there is an increase in aldosterone 25 secretion. Hypertension is always present in Conn's Syndrome.

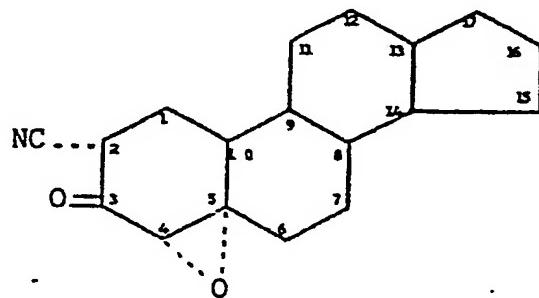
It is believed that trilostane is of value in the

above treatments due to its ability to act as an anti-hypertensive, especially in those patients where hypertension is associated with high aldosterone and low renin; low aldosterone and low renin; high aldosterone and high renin.

Prior to the present invention, the use of trilostane and related compounds met with unsatisfactory results because previous formulations gave variable absorption characteristics and unpredictable blood levels. Thus, previous formulations of trilostane have been found to be unreliable in the treatment or control of symptoms in those conditions mentioned above due to variations in availability of trilostane in vivo.

We have now found that by processing raw trilostane and related compounds to bring their particle size within a particular narrow range, pharmaceutical compositions can be prepared which exhibit for their active ingredient improved absorption characteristics and which can avoid or substantially avoid the unsatisfactory results given by previous formulations. Despite the fact that in in vitro testing products containing batches of trilostane of differing particle sizes could not be differentiated in respect of their dissolution or release properties, control of particle size has been shown to produce, as described in more detail below, a significant improvement in plasma concentration in vivo.

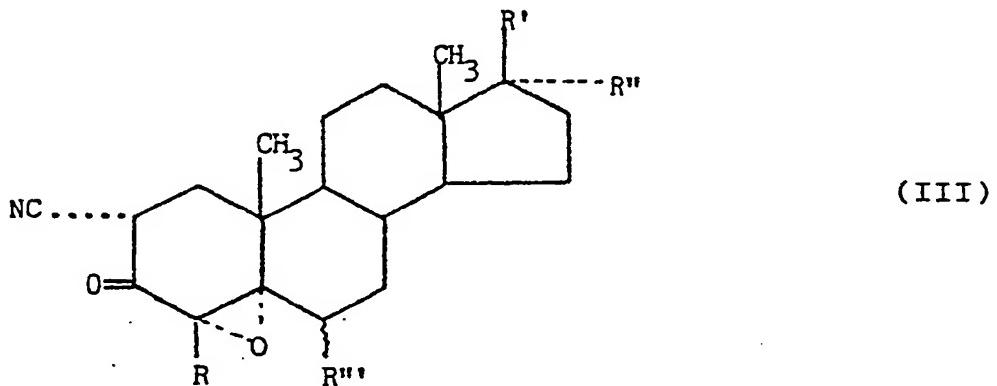
Accordingly, the present invention provides, in particular for use in preparing pharmaceutical compositions having improved absorption characteristics, a 2α -cyano- 4α , 5α -epoxy- 3α -oxo-steroid compound having a basic ring structure of the general formula:



the compound being in particulate form and consisting of particles having a mean equivalent sphere volume diameter of less than about 20 μm , at least 95% of the particles having a particle size of less than about 5 50 μm .

In one aspect of the invention, the particulate compound may be a compound of the above formula II of the kind described in British Patent Specification No. 1,123,770, that is to say a 2 α -cyano-4 α ,5 α -epoxy-3-10 oxo-steroid in which the steroid moiety has from 19 to 23 carbon atoms exclusive of ester radicals.

Alternatively, in another aspect of the invention the particulate compound may be a compound of the above formula II of the kind described in British Patent Specification No. 2,010,278A, that is to say a 2 α -cyano-4 α ,5 α -epoxy-3-oxo-steroid having the general formula:



wherein R is hydrogen or methyl;

R' is hydroxy or lower-alkanoyloxy;

R'' is hydrogen, lower-alkyl, lower-alkenyl or lower-20 alkynyl;

or R' or R'' together represent oxo or ethylenedioxy;

R''' is hydrogen or methyl;

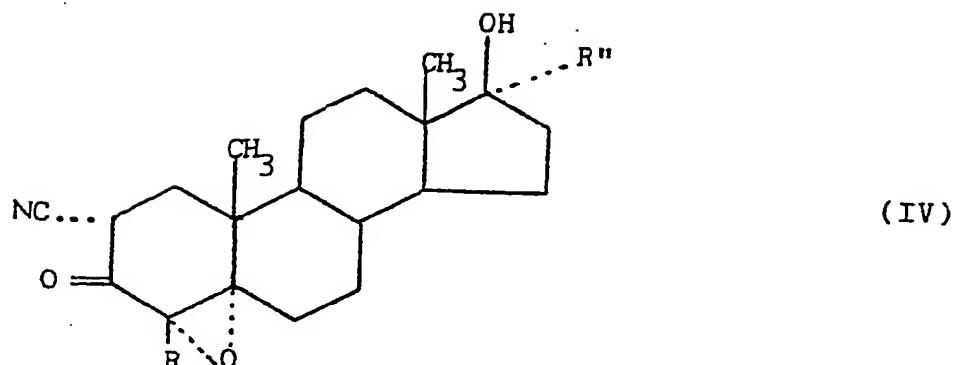
or 3-enol lower-alkanoate esters thereof;

with the proviso that when R is hydrogen, R''' is

25 α -methyl, and when R is methyl, R''' is hydrogen or β -methyl, which compounds are disclosed as being useful as interceptive agents, that is in disrupting pregnancy when administered to pregnant female mammals.

Preferably, the compound of the invention is a 30 compound of the general formula:

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wherein R is hydrogen or methyl and R'' is hydrogen or lower alkyl, especially methyl.

Most preferably the compound of the invention is trilostane, i.e. a compound of formula (IV) wherein R and R'' are both hydrogen; or a compound of formula (IV) wherein R and R'' are both methyl. It is believed the invention is particularly applicable to those two specific compounds, and in particular the former compound, trilostane.

Preferably, the particulate compound of the invention consists of particles having a mean equivalent sphere volume diameter of about 12 μm or less, with a preferred lower limit being about 4 to about 5. More preferably, the mean equivalent sphere volume diameter of the particles should be about 10 μm or less e.g. from about 5 to about 10 μm , and still more preferably above 5 μm , at least 95% of particles always having a particle size of less than 50 μm .

(It will of course be understood by those familiar with comminution process techniques that the limit set on the size of 95% or more of the particles is a subsidiary limitation necessary additionally to distinguish the particulate compounds of the invention from those exhibiting a broader size distribution, because of the wide variation in size encountered in all powders reduced in size by a process of comminution or particle size reduction, for example, by milling utilising a variety of kinds of milling equipment now available, for example, hammer, pin or fluid energy mills.)

The invention also provides pharmaceutical compositions comprising the said particulate compound of the invention and one or more pharmaceutically-acceptable excipients or carriers.

Such excipients or carriers may be solid, semi-

solid or liquid as appropriate to the pharmaceutical form chosen, and may include a wide range of organic and inorganic solids, semi-solids and aqueous and non-aqueous liquids. Of these there may be used, for
5 example, talc, gum arabic, starch, lactose, magnesium stearate or fatty substances of animal or vegetable origin such as cocoa butter, lanolin derivatives, paraffin derivatives or glycols. These excipients or carriers may be compounded with one or more wetting, dispersing or emulsifying agents and/or one or more preservatives as desired. Thus, the compositions of the
10 invention may be presented as a tablet, capsule, granulate for suspension, cream, ointment, suppository or suspension.

15 Preferably the composition of the invention includes a solid excipient or carrier with which the said particulate compound of formula (II) is mixed, for example, starch, lactose and/or magnesium stearate.

More preferably, the composition is presented as a
20 tablet or in an encapsulated form, the particulate compound of formula (II), together with any excipient or carrier being filled into the shell of a capsule. Preferably, the capsule contains active compound and diluent in a ratio of about 1:3.

25 Typically, the composition of the invention when in unit dosage form may comprise a unit dose of from about 50 to about 250 mg of the compound of formula (II), for example, about 60 mg, about 120 mg and about 240 mg, and more preferably about 50 to about 120 mg.

30 Preferably the particulate compound of formula (II) is also one in which the specific surface area is at least about $2\text{m}^2 \text{ g}^{-1}$ e.g. 2 to 4 $\text{m}^2 \text{ g}^{-1}$.

The invention also includes a method of treating a steroid compound having a basic ring structure of the
35 general formula (II) shown above, which method comprises processing the raw steroid compound in a treatment which reduces its particle size so as to produce a compound in particulate form and consisting of particles having a mean equivalent sphere volume diameter of less than about 20 μm , at least 95% of the particles having a particle size of less than about 50 μm .

In preparing the particulate compound of the invention a compound of formula (II), in its raw state, is first characterised for size using an instrument

adapted to measure equivalent sphere volume diameter, that is to say a Coulter Counter. Typically a representative sample of a compound of formula (IV) where R and R'=H would be expected to comprise in its raw state particles having a mean equivalent sphere volume diameter of about 40 μm and with a broad size distribution.

After being characterised for size in its raw state, the raw compound is then milled, preferably using a fluid energy (air) mill, under suitable conditions e.g. of air pressure and feed rate, to bring the particle size value within the above-mentioned limits according to the invention. The efficiency of the milling is checked by sampling using a Coulter Counter and the final particle size is checked in a similar manner. If a first pass through the mill does not produce the required size spectrum, then one or more further passes are effected.

The compound of formula (II) in its particulate form within the above-mentioned limits according to the invention may then be mixed with an excipient or carrier as necessary and, for example, filled into capsules. Thus, for example, the particulate compound may be mixed with maize starch and lactose, granulated with water, dried, terminally blended with magnesium stearate, and filled into capsules.

Because the particles obtained by milling or other particle size reduction techniques are irregular in shape, it is necessary to characterise them not by measurement of an actual size such as thickness or diameter, but by measurement of a property of the particles which is related to the same property when possessed by a theoretical spherical particle. The particles are thus allocated an "equivalent sphere diameter".

The values found from characterising a large number of "unknown" particles can be plotted number vs. diameter or in other methods weight vs. diameter, usually adopting percentage oversize values for number or weight. This gives a characteristic curve representing size distribution of the sample, i.e. a cumulative percentage oversize distribution curve. Values from this can be read off directly or plotted on log-probability paper to give an approximately straight

line. The mean equivalent sphere volume diameter is the 50% oversize value and the slope of the line is related to the standard deviation (s.d.) of the distribution. For convenience this may be calculated from the values at 84.1% and 15.9% oversize together with the mean equivalent sphere volume diameter thus:

Mean equivalent sphere volume diameter
(=50% oversize)

5 s.d. =
$$\frac{\text{Diameter at } 84.1\% \text{ oversize}}{\text{Diameter at } 15.9\% \text{ oversize}}$$

10 or
$$\frac{\text{Diameter at } 15.9\% \text{ oversize}}{\text{Mean equivalent sphere volume diameter}}$$

15 s.d. =
$$\frac{\text{Mean equivalent sphere volume diameter}}{(\text{=50% oversize})}$$

The above applies for a log normal distribution, which may acceptably be assumed for milled powder samples. Typically, a particulate compound according to the invention will give a standard deviation of about 2 μ m.

20 The mean equivalent sphere volume diameter found is thus a statistical representation of a theoretical particle having the same property as the "unknown" particles .

25 As indicated above the mean equivalent sphere volume diameter of the particles of the milled compound of formula (II) may be evaluated using a Coulter Counter. Using such an instrument values for a suspension of the particles of unknown size may be obtained and the Counter may be calibrated using a 30 standard suspension of latex particles within the size range expected for the particles of unknown size. In the case of standard latex particles values of standard deviation are extremely small because of the "sieve cut" nature or very uniform particle size.

35 Following is a description by way of example of the preparation of compositions in accordance with the invention. In all of the Examples the trilostane was prepared from a raw form using a fluid energy (air) mill and consisted of particles having a mean equivalent sphere volume diameter of about 10 μ m, at least 95% of the particles having a particle size of less than about 50 μ m. The particle size of the reduced trilostane was measured as follows:

First a small sample was checked under a

microscope and a visual assessment made both of the size of the particles against a standard calibration scale, e.g. say predominantly about $10\mu\text{m}$, and of the uniformity of particle size. These visual assessments 5 indicating acceptable parameters, that is most particles being within the desired size range and size distribution, a further sample of the reduced material was subjected to particle size measurement using a Coulter Counter TAII by the procedure given below.

10 Alternatively, if the small sample visual check gave an estimated size or size distribution outside the desired specification, the milling conditions were adjusted.

The Coulter Counter particle size measurement was effected on a 5 mg sample of the reduced material, the 15 sample being suspended in approximately 100 ml of electrolyte, for example, Isoton II. Prior to the sample suspension the electrolyte was saturated with micronised material, the pH of the resultant solution was adjusted to about 3.5, and the solution was filtered through a 20 $0.22\mu\text{m}$ microporous membrane filter to provide the necessary particle-free suspending electrolyte.

The electrolyte solution contained one drop of Coulter dispersant and dispersion was effected using an ultrasonic bath treatment for approximately one minute. 25 The suspension was then diluted to approximately 200 ml with Isoton II and treated again in the ultrasonic bath for approximately one minute. The acceptability of the dispersion concentration was checked using a preset count of 70,000 particles with an aperture of $140\mu\text{m}$ 30 (satisfactory for 5 to $10\mu\text{m}$ mean equivalent sphere volume diameter particles) to give a reading of less than 10% on the calibration scale. (In any size analysis technique, because the particles are of differing size, it is necessary to characterise a large 35 number for statistical accuracy of the result. The value of 70,000 is that chosen in this case.)

The tube aperture in the Coulter Counter is chosen depending on the expected particle size values. Greatest result accuracy is obtained when the particle 40 diameters are from 4 to 40% of the aperture size to avoid false counts and disturbance. A calibration scale of 10% is a Coulter Electronics recommendation of no significance to the size).

Within ten minutes of the preparation of the

dispersion, duplicate counts were performed. Duplicate counts are effected as a minimum check a) to produce more reliable measurements and b) to check that equipment sampling of the suspended material has been reproducible i.e. the suspension has not settled.

The checked results were automatically recorded and displayed graphically to give a cumulative percentage oversize versus size characteristic curve for the sample. From this, the mean equivalent sphere volume diameter value was derived (50% oversize value) together with the standard deviation of the distribution calculated as described above.

The standard deviation was the expected value of approximately 2.0 μm , the limit being between about 1.8 μm and about 2.5 μm on ten batches.

The Coulter Counter was calibrated as follows:

A suspension of standard Coulter Electronics latex particles of stated mean diameter of 13.7 μm was treated as above using an aperture and equipment settings as described. The mean value derived was between 12.5 and 14.5 μm when the Counter was correctly calibrated.

Compositions were then prepared as follows:

Example 1

<u>Capsules:</u>	<u>Formulations</u>	<u>60 mg</u>	<u>120 mg</u>
25	Trilostane	60 mg	120 mg
	Lactose	86 mg	172 mg
	Maize starch	86.65 mg	173.3 mg
	Magnesium stearate	2.35 mg	4.7 mg
30		235 mg	470 mg

Preparation

These formulations are prepared by either conventional dry blending techniques or more preferably conventional wet granulation techniques. Encapsulation is effected by means of conventional equipment.

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		<u>Example 2</u>		
<u>Tablets</u>		<u>Formulations</u>	<u>60 mg</u>	<u>120 mg</u>
5	Trilostane	60 mg	120 mg	240 mg
	Lactose	80 mg	160 mg	320 mg
	Maize starch	85 mg	170 mg	340 mg
	Magnesium stearate	2 mg	4 mg	8 mg
		<u>227 mg</u>	<u>454 mg</u>	<u>908 mg</u>

Preparation

10 The powders are granulated by means of conventional wet granulation techniques. The tablets are compressed using conventional compression equipment to tablet or caplet form.

		<u>Example 3</u>		
<u>Suppositories:</u>		<u>Formulations</u>	<u>60 mg</u>	<u>120 mg</u>
	Trilostane	60 mg	120 mg	240 mg
	Suppository base	qs	qs	qs

Preparation

The suppositories are prepared from a suitable suppository base (e.g. Suppocire, Witepsol, Novata, etc.) using conventional poured melt techniques or cold

25 compression.

		<u>Example 4</u>		
<u>Ointment:</u>		<u>Formulations</u>	<u>1%</u>	<u>2.5%</u>
	Trilostane	1%	2.5%	5%
	Ointment base	to 100%	to 100%	to 100%

Preparation

30 The ointments are prepared by incorporating the trilostane into a suitable pre-prepared ointment base (e.g. white soft paraffin).

		<u>Example 5</u>		
<u>Cream</u>		<u>Formulation</u>	<u>1%</u>	<u>2.5%</u>
	Trilostane	1%	2.5%	5%
	Cream base	to 100%	to 100%	to 100%

Preparation

40 The creams are prepared by incorporating the trilostane into a suitable pre-prepared cream base (e.g. aqueous cream B.P.)

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Example 6

<u>Suspension</u>	<u>Formulations</u>	<u>1.2%</u>	<u>2.4%</u>	<u>4.8%</u>
	Trilostane	1.2%	2.4%	4.8%
	Citric acid			
5	(anhydrous) BP	0.237%	0.237%	0.237%
	Sorbitol			
	solution BPC	20%	20%	20%
	Cetomacrogol			
10	1000 BPC	0.09%	0.09%	0.09%
	Sodium			
	phosphate BP	0.63%	0.63%	0.63%
	Sodium carboxy-			
	methyl cellulose	0.20%	0.20%	0.20%
15	Veegum K	1.00%	1.00%	1.00%
	Flavour	qs	qs	qs
	Preservative	qs	qs	qs
	Purified water	to 100%	to 100%	to 100%

Preparation

The suspensions are prepared by conventional manufacturing techniques having regard to the processing properties of the ingredients. Finally, each suspension is passed through a homogeniser.

Bioavailability Test:

60 mg capsules were prepared as described in Example 1 by wet granulation techniques using batches of trilostane comprising (i) particles having a mean equivalent sphere volume diameter of about 10 μm (at least about 95% of the particles having a particle size of less than about 50 μm), (ii) particles of mean equivalent sphere volume diameter of about 45 μm , and (iii) particles of mean equivalent sphere volume diameter greater than 100 μm .

In a three part double blind cross-over study on eight volunteers, each volunteer received a dosage of 120 mg of trilostane (2 x 60 mg capsules) on an empty stomach with 50 ml of tap water. Blood samples (8 ml) were taken pre-medication and at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0 and 24.0 hours and assayed for plasma levels of trilostane and trilostane metabolite. Plasma concentrations were processed by a computer programme giving maximum concentration in plasma (C_{\max}) and time taken to reach this maximum (T_{\max}) by inspection. Values for the area under the curve of concentration against time over the time span 0 to t

(AUC_0^t - where t is time) were then calculated using the trapezoid rule and statistical analysis was carried out using the Students paired t-test.

In most cases, plasma levels could not be detected at 24 hours and consequently AUC_0^{24} could be used to assess the extent of absorption. The following Table I sets out AUC_0^{24} values ($\text{mg.ml}^{-1}.\text{h}$) for trilostane and 17-keto metabolite.

TABLE I

Particle size	10 μm	45 μm	100 μm
Trilostane AUC_0^{24}	1.6	0.6	0.2
Metabolite AUC_0^{24}	5.0	2.7	1.3

As can be seen from the above results, plasma trilostane and metabolite concentration are dependent on the particle size of trilostane used, the smallest particle size material, i.e. that according to the invention, giving rise to the highest plasma concentrations. Plasma metabolite concentrations followed the time course of trilostane concentrations very closely but at a level of 2 to 3 times higher. In addition, the ratio of Metabolite AUC_0^{24} to Trilostane AUC_0^{24} for the 10 μm , 45 μm and 100 μm materials is respectively 3.1, 4.5 and 6.5.

Thus, the lower AUC_0^{24} values for the larger particle size capsules indicate that the extent of absorption from those capsules was reduced. Furthermore, with the smallest particle size material there is a highly favourable ratio of trilostane active material to trilostane metabolite.

Accordingly, the results given above indicate clearly that the particle size of trilostane used in the formulations had a very pronounced influence on the availability of trilostane in plasma. The capsules containing 10 μm material resulted both in high plasma trilostane and metabolite concentrations, as well as a favourable ratio of trilostane to metabolite. However, an increase in particle size of trilostane to approximately 45 μm and then to greater than 100 μm resulted in successive reductions in the plasma concentration levels, as well as in significant increase

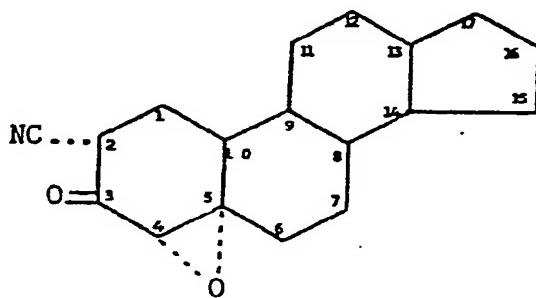
in the ratio of metabolite to active material.

In our co-pending British Patent Application No. 83-
5 III in which, in particular, R is methyl, R' is hydroxy and R" is methyl, having a reduced particle size inter alia as defined herein, which method comprises dissolving the compound in an organic solvent, preferably dimethylformamide, precipitating the compound by mixing a non-solvent for the compound, preferably water, with the said solution, and controlling the mixing conditions to produce a precipitate having the desired reduced particle size.

10 It is to be understood that in preparing a compound of the formula III in accordance with the present invention in which, in particular, R is methyl, R' is hydroxy and R" is methyl, it is preferred to employ the method of our co-pending Application.

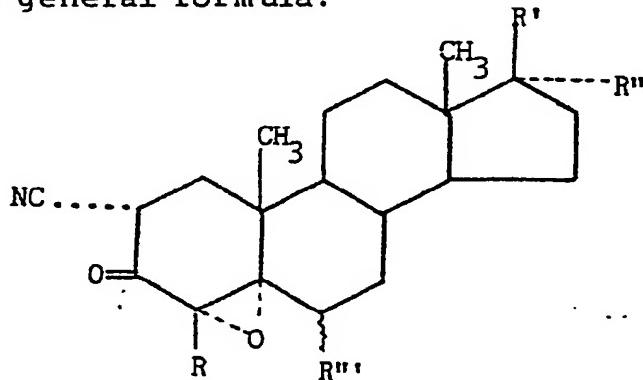
CLAIMS

1. A 2α -cyano $4\alpha,5\alpha$ -epoxy-3-oxo-steroid compound, preferably having from 19 to 23 carbon atoms exclusive of ester radicals, the basic ring structure of the steroid being of the general formula:



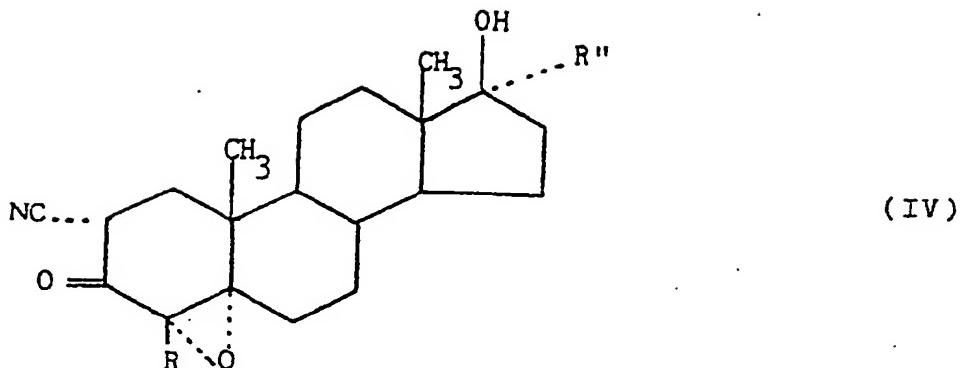
(II)

- 5 characterised in that the compound is in particulate form and consists of particles having a mean equivalent sphere volume diameter of less than about $20\mu\text{m}$, at least 95% of the particles having a particle size of less than about $50\mu\text{m}$.
- 10 2. A particulate compound according to claim 1 either of the general formula:



(III)

- wherein R is hydrogen or methyl;
R' is hydroxy or lower-alkanoyloxy;
R'' is hydrogen, lower-alkyl, lower-alkenyl or lower-alkynyl;
15 or R' or R'' together represent oxo or ethylenedioxy;
R''' is hydrogen or methyl;
or 3-enol lower-alkanoate esters thereof;
with the proviso that when R is hydrogen, R''' is α -methyl, and when R is methyl, R''' is hydrogen or β -methyl,
- 20 or of the general formula:



wherein R is hydrogen or methyl and R'' is hydrogen or lower alkyl.

3. A particulate compound according to claim 2, wherein R and R'' are either both hydrogen or both methyl.

4. A particulate compound according to any one of the preceding claims, wherein the particles have a mean equivalent sphere volume diameter of about 12 μm or less, preferably about 10 μm or less.

5. A particulate compound according to claim 4, wherein the mean equivalent sphere volume diameter of the particles is from about 5 to about 10 μm , and preferably above 5 μm .

6. A particulate compound according to any one of the preceding claims, wherein its cumulative percentage oversize versus size characteristic curve exhibits a standard deviation of about 2 μm .

7. A particulate compound according to any one of the preceding claims, wherein its specific surface area is about 2 m^2g^{-1} or higher.

8. A particulate compound according to any one of the preceding claims, wherein the mean equivalent sphere volume diameter is measured using a Coulter Counter.

9. For use in preparing pharmaceutical formulations exhibiting improved absorption characteristics for active ingredient and a higher active ingredient to metabolite ratio, a compound of the general formula (II) defined in claim 1 and according to any one of the preceding claims.

10. A method of treating a steroid compound having a basic ring structure of the general formula II shown in claim 1, which method comprises processing the raw steroid compound in a treatment which reduces its particle size so as to produce a compound in particulate

form and consisting of particles having a mean equivalent sphere volume diameter of less than about 20 μm , at least 95% of the particles having a particle size of less than about 50 μm .

- 5 11. A pharmaceutical composition, which composition comprises a particulate compound according to any one of claims 1 to 8 and one or more pharmaceutically-acceptable excipients or carriers, preferably in the form of a tablet, a capsule, a granulate for suspension,
10 a cream, an ointment, a suppository or a suspension, more preferably in encapsulated form, the particulate compound of formula (II), together with excipient or carrier being filled into the shell of a capsule, and
15 the capsule containing active compound and diluent in a ratio of about 1:3.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application number

EP 83 30 6665

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ?)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X, Y	US-A-3 296 255 (RAYMOND O. CLINTON) * Claims 1,10-13,15; column 3 *	1-3,11	C 07 J 71/00 A 61 K 31/58
X, Y D	--- GB-A-1 123 770 (STERLING DRUG) * Claims 1-8; page 2 *	1-3,11	
X, Y D	--- GB-A-2 010 278 (STERLING DRUG) * Claims 1-13,35 *	1-3,11	
Y	--- US-A-4 196 188 (JEAN-LOUIS A. BESINS) * Whole document *	8,9,11	
Y	--- CHEMICAL ABSTRACTS, vol. 88, no. 11, 13th March 1978, page 69, no. 69434d, Columbus, Ohio, US L.A. RIGG et al.: "Efficacy of intravaginal and intranasal administration of micronized 17beta-estradiol" & J. CLIN. ENDOCRINOL. METAB. 1977, 45(6), 1261-4 * Abstract *	8,9,11	TECHNICAL FIELDS SEARCHED (Int. Cl. ?)
	---	-/-	C 07 J A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 30-01-1984	Examiner HENRY J.C.	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			



DOCUMENTS CONSIDERED TO BE RELEVANT			Page 2								
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ?)								
Y	<p>CHEMICAL ABSTRACTS, vol. 96, no. 5, 1st February 1982, page 87, no. 28862p, Columbus, Ohio, US</p> <p>G.T. McINNES et al.: "Bioavailability and pharmacological activity of micronized and nonmicronized spironolactone in healthy men" & C.-R. - CONGR. EUR. BIOPHARM. PHARMACOCINET., 1 st 1981, 1, 212-21 * Abstract *</p> <p>-----</p>	8,9,11									
The present search report has been drawn up for all claims											
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">Place of search</td> <td style="padding: 2px;">Date of completion of the search</td> <td colspan="2" style="padding: 2px;">Examiner</td> </tr> <tr> <td style="padding: 2px;">THE HAGUE</td> <td style="padding: 2px;">30-01-1984</td> <td colspan="2" style="padding: 2px;">HENRY J.C.</td> </tr> </table>				Place of search	Date of completion of the search	Examiner		THE HAGUE	30-01-1984	HENRY J.C.	
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